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FILE CONTENT:1840 - 14 Dec 2010 VOL 153 ISS 25

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L2                  STR
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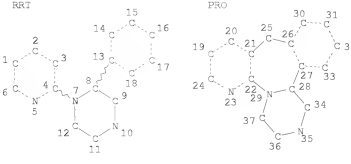


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RING(S) ARE ISOLATED OR EMBEDDED
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L4            24 SEA FILE=CASREACT SSS FUL L2 (    74 REACTIONS)

100.0% DONE      74 VERIFIED      74 HIT RXNS                  24 DOCS
SEARCH TIME: 00.00.01


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L4 ANSWER 1 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 151:501499 CASREACT
TI Process for the preparation of 1-(3-hydroxymethylpyrid-2-yl)-2-phenyl-4-methylpiperazine and mirtazapine
IN Bhatu, Manjunath Narayani Naik, Samrit Joshi, Prashant; Sharma, Vijay
PA Watson Pharma Private Limited, India
SO PCT Int. Appl., 24pp.
CODEN: PIXXD2
CT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO-2010064511	A1	20100610	2009WO-IN050415	20090211
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, BW, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GH, GM, GR, HR, HU, IE, IS, IT, KE, LS, LT, LU, LV, MC, MW, MZ, NA, NL, NO, OA, PL, PT, RO, RS, SD, SE, SI, SK, SL, SM, ST, SZ, TR, TZ, UG, ZM, ZW				
19--2201			2008IN-DEL02201	20081022
20--2279			2008IN-DEL02279	20081022

ORAI 1361b-200021278 ISORIS2010
AB The invention relates to the process for the manufacture of mirtazapine and intermediates useful in preparing mirtazapine. Mirtazapine was prepared via cyclization of 1-(3-cyanopyridyl-2-methyl)-3-phenylpiperazine; the resulting 1-(3-carbopyridyl-2-methyl)-3-phenylpiperazine underwent reduction to give 1-(3-hydroxymethylpyridyl-2)-4-methyl-3-phenylpiperazine, which underwent cyclization to give the title compound

RX(3) OF 6

(step 1)

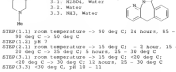
CON: STAGE(1) room temperature -> 15 deg C; <15 deg C; 2 hours, 15 - 30 deg C
STAGE(2) 30 deg C -> 50 deg C; 12 hours, 25 - 30 deg C
STAND(3) >25 deg C; pH 10 - 11

L4 ANSWER 1 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(5) OF 6 - 3 STEPS

CON: STAGE(1.1) room temperature -> 15 deg C; -1 hour, 15 - 20 deg C; 30 deg C -> 15 deg C; 5 hours, 15 - 30 deg C
STAGE(1.2) 30 deg C -> 50 deg C; 12 hours, 25 - 30 deg C
>28 deg C -> 30 deg C; 12 hours, 25 - 30 deg C
STAGE(1.3) <30 deg C; pH 10 - 11

RX(4) OF 6 - 3 STEPS

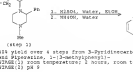


CON: STAGE(1.1) room temperature -> 90 deg C; 24 hours, 85 - 90 deg C; 90 deg C -> 50 deg C
STAGE(1.2) 50 deg C
STAGE(2.1) room temperature -> 15 deg C; -2 hours, 15 - 20 deg C; 20 deg C -> 25 deg C; 4 hours, 25 - 30 deg C
STAGE(2.1) room temperature -> 15 deg C; <20 deg C; <28 deg C -> 30 deg C; 12 hours, 25 - 30 deg C
STAGE(3.3) <30 deg C; pH 10 - 11

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 151:439844 CASREACT
TI Improved synthesis of mirtazapine
AU Shengqiang, Zhang; Yuanyuan, Hou; Hongyan; Cui, Tingtao; Liu, Dan
CS Meihua Pharmaceutical Co., Ltd., Harbin, Heilongjiang Province, 150028, Peop. Rep. China
SO Shengyao Xuebao Huaxue Zazhi (2009), 18(5), 350-352
CODEN: SYHZEF; ISSN: 1005-1104
PB Shengyao Xuebao Huaxue Zazhi Bianjibu
DT Journal
LA Chinese
AB The synthetic procedure of antidepressant mirtazapine [1,e.,1,2,3,4,10,14b-octaazydro-2-methylpyrazino[1,2-a]pyrido[2,3-c][2]benzazepine] was improved. The key intermediate 1-(3-cyanopyridyl-2-methyl)-3-phenylpiperazine as the starting materials, mirtazapine was obtained by a synthetic sequence involving an alkylation, hydrolysis, reduction and intramol. Friedel-Crafts alkylation. The structure of mirtazapine was confirmed by elemental anal., IR, NMR, LTC-MMR, MS. Compared with the literature procedure, the improved synthetic route above-mentioned optimized each reaction process was simple and suitable for industrial production with lower cost and higher yield. The overall yield was improved from 40% to 45%.

RX(4) OF 10



(step 3)

NOTE: 60% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-[3-methylphenyl]-
CON: STAGE(1) room temperature; 1 hours, room temperature
STAGE(2) pH 9

RX(7) OF 10 - 2 STEPS

NOTE: 2: 60% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-[3-methylphenyl]-
CON: STAGE(1) room temperature; 4 hours, reflux
STAGE(2) room temperature; 2 hours, room temperature
STAGE(2) pH 9

L4 ANSWER 2 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS

NOTE: 3) 40% yield over 4 steps from 3-Pyridinecarbonitrile, 2-chloro- and Piperazine, 1-[3-methylphenyl]-
CON: STAGE(1) room temperature -> 180 deg C; 24 hours, 100 deg C
STAGE(2.1) room temperature; 4 hours, reflux
STAGE(2.2) room temperature; 2 hours, room temperature
STAGE(3.3) pH 9

L4 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
AN 152:356869 CAPLUS
TI Preparation method of mirtazapine and its intermediates
IN Wan, Xingang, Zu, Xianjie, Wang, Anzhen, Zhang, Haifan, Lu, Haibo
PA Watson Pharmaceuticals Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongbao Shuomingshu, 11pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN-----101814016	A	20100825	201047A-101814016	20090824
PRAI 201047A-101814016		20090824		

OS MARPAT 152:356869
AB Title extraction relates to the preparation method of mirtazapine. The preparation method of mirtazapine comprises: (1) 1-(2-chlorophenyl)-1-(3-pyridyl)-4-methyl-3-phenylpentanol (II, I is prepared by reducing II in solvent at (-20)-35°C with reducing agent. The reducing agent may be sodium borohydride, lithium borohydride, potassium borohydride, lithium aluminum hydride, and/or sodium bis(2-methoxyethoxy)aluminum hydride; (2) II is prepared by esterifying 1-(3-carboxy-2-hydroxyl-4-methyl-3-phenylpentane, or by reacting 2-halo-1-(chlorophenyl)pyridine with 1-methyl-3-phenylpersine in the presence of EE, NaH, or KI. This inventive method is simple, safe, convenient, and fit for com. process.

RX(5) OF 12

CON: STAGE(1) 4 hours, 35 deg C
STAGE(2) 29 - 30 deg C, pH 8 - 9

RX(9) OF 12 - 3 STEPS

CON: STEP(1-3) 4 hours, reflux; reflux -> 35 deg C
STEP(2-3) 4 hours, 35 deg C
STEP(1-2) 30 - 90 deg C, pH 8 - 9

L4 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
AN 152:131840 CAPLUS
TI Synthesis of 1,2,3,4,5,10b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]-2-benzazepine and its intermediate
AU Shang, Zhuowei, Xu, Xiaojian, Xu, Huilin
CS Shanghai Institute of Pharmaceutical Industry, Shanghai, 200437, Peop. Rep. China
SO Zhongguo Yiyao Gongye Zazhi (2009), 37(10), 653-654
CODEN: ZYGZAS; ISSN: 1001-8255
PB Zhongguo Yiyao Gongye Zazhi Bianjibu
DT Journal
LA Chinese
AB A method for the synthesis of the title compound is reported here. 1-Benzyl-4-methylpiperazine-2-one was reduced to 1-benzyl-2-methylpiperazine (I, R = H) by a Red-Al reagent. I was condensed with 2-(2-nitrobenzyl)-3-pyridinecarboxylic acid (II) by reduction with diborane generated in situ (sodium borohydride/HCl gas or sodium borohydride/BF3.OEt2) to provide 3-(4-benzyl-2-phenyl-1-piperazinyl)-3-pyridinemethanol. A subsequent acid-mediated cyclization and purification of the latter provided the above-mentioned mirtazapine (63% overall yield).

RX(2) OF 3

NOTE: 61% yield over 2 steps from
3-((benzyl)(2-phenyl-2-piperazinyl)-3-Pyridinecarboxylic acid
CON: STAGE(1) 30 deg C, 7 hours, pH ~ 40 deg C
STAGE(2) pH 1 ~ 2, pH 11

RX(3) OF 3 - 2 STEPS

NOTE: 1) alternative reaction conditions shown. 2) 61% yield over 2 steps from
3-((benzyl)(2-phenyl-2-piperazinyl)-3-Pyridinecarboxylic acid
CON: STEP(1) 30 deg C, 7 hours
STEP(1.1) 0 - 5 deg C, 5 deg C -> 40 deg C; 2 hours, 40 deg C; 40 deg C -> 5 deg C
STEP(1.2) 170 deg C
STEP(1.3) 55 deg C
STEP(1.4) 55 deg C
STEP(2.1) 50 deg C; 7 hours, 30 - 40 deg C
STEP(1.2) pH 1 ~ 2; pH 11

L4 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN (Continued)

RX(10) OF 12 - 3 STEPS

NOTE: 1) incremental addition of ethanol and sulfuric acid
CON: STEP(1.1) 2 hours, reflux; 80 deg C; 1 hour, reflux
STEP(1.2) reflux; reflux -> 35 deg C
STEP(2.1) 4 hours, 35 deg C
STEP(3.1) 20 - 30 deg C, pH 8 - 9

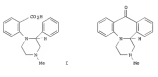
RX(11) OF 12 - 3 STEPS

CON: STEP(1.1) room temperature -> 100 deg C; 4 hours, 100 deg C
STEP(2.1) 4 hours, reflux; reflux -> 35 deg C
STEP(2.2) 4 hours, 35 deg C
STEP(3.1) 20 - 30 deg C, pH 8 - 9

L4 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
AN 149:473563 CAPLUS
TI Method for the preparation of an enantiomer of a tetracyclic azaazepine compound, having mirtazapine activity, via cyclization and reduction reactions
IN Kempegowda, Sekarakoi Jobanpura
PA M.V. Organics, Retch.
SO U.K. Pat. Appl. Publ., 9pp.
CODEN: UKXXGO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI GB-2008015858	A1	20081016	2008GB-00015858	20080107
PRAI 2007GB-0002880P		20070411		

GI



AB The present invention relates to a method for the preparation of mirtazapine and tetracyclic analogous compds. having substantial enantiomeric excess of the R or S form. The invention further relates to a novel intermediate for the preparation of mirtazapine and tetracyclic analogous having enantiomeric excess of the R or S form. The method comprising the steps of (a) providing a carboxylic acid I having enantiomeric excess of the S or R form, (b) converting the carboxylic acid group of I into a ketone II, (c) optionally reducing II with a mild reduction agent to form the intermediate epoxy III, (d) forming the mirtazapine IV by reduction of II or III using a strong reduction agent

RX(5) OF 34

NOTE: alternative preparation shown, incremental addition, stereoselective
CON: STEP(1.1) 0 deg C, 75 minutes, room temperature
STEP(2.1) 4 hours, 0 deg C; room temperature

RX(13) OF 34 - 2 STEPS

NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective
CON: STEP(1.1) room temperature -> 62 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 4 hours, 0 deg C; room temperature

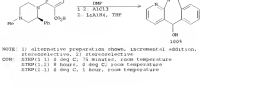
RX(13) OF 34 - 3 STEPS

NOTE: 1) alternative preparation shown, incremental addition, stereoselective, 2) stereoselective, worksp
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(2.1) 4 hours, 0 deg C; room temperature
STEP(2.1) 0 deg C; 15 minutes, 50 deg C

RX(16) OF 34 - 4 STEPS

NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective
CON: STEP(1.1) room temperature -> 57 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 4 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 1 hour, room temperature
STEP(4.1) 0 deg C; 15 minutes
STEP(4.2) 18 hours, 50 deg C

RX(14) OF 34 - 2 STEPS



NOTE: 1) alternative preparation shown, incremental addition, stereoselective, 2) stereoselective
CON: STEP(1.1) 0 deg C; 75 minutes, room temperature
STEP(2.1) 4 hours, 0 deg C; room temperature
STEP(2.1) 0 deg C; 1 hour, room temperature

RX(21) OF 34 - 3 STEPS

NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective, worksp
CON: STEP(1.1) room temperature -> 62 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 4 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 1 hour, room temperature

RX(22) OF 34 - 3 STEPS

NOTE: 1) stereoselective, 2) alternative preparation shown, incremental addition, stereoselective, 3) stereoselective
CON: STEP(1.1) room temperature -> 62 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 4 hours, 0 deg C; room temperature
STEP(3.1) 0 deg C; 1 hour, room temperature

AN 149147283 CAPLUS
TI Preparation of enantiomers of tetracyclic benzazepines
IN Preparation Enterprises Inc.
PA N.V. Organon, Netherlands
SO PCT Int. Appl., 19pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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	WO---2008125578	A3	20090108		
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	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
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	AR---------066205	A1	20090715	2008AR-APP0101576	20080418
	EP---------2136808	A2	20091231	2008EP-08736838	20080418
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	2008WO-EP055136		20080418		
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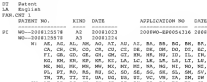
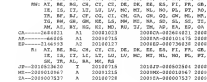




AB The present invention relates to a method for the preparation of mitazapine and tetracyclic analogues compds. having substantial enantiomeric excess of the S or R form. The method comprises the steps of (a) providing a carboxylic acid compound according to Formula I having a substantial enantiomeric excess of the S or R form; (b) converting the carboxylic acid group into ketone group to give ketone compound II, (c) optionally reducing ketone compound II with a mild reduction agent to form the intermediate hydroxy compound

L4 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 20 - 2 STEPS

NOTE: alternative preparation shown, incremental addition
CON: STAGE(1) 0 deg C; 75 minutes, room temperature
STAGE(2) 0 deg C; 8 hours

RX(8) OF 20 - 3 STEPS

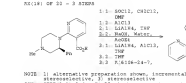
NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition
CON: STEP(1) room temperature -> 50 deg C; 3 days, reflux
STEP(2) 1) 0 deg C; 75 minutes, room temperature
STEP(2) 2) 0 deg C; 8 hours

RX(10) OF 20 - 2 STEPS

NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective
CON: STEP(1) 1) 0 deg C; 75 minutes, room temperature
STEP(1) 2) 0 deg C; 8 hours
STEP(2) 1) 0 deg C; 10 hours
STEP(2) 2) 0 deg C
STEP(2.1) pH 14

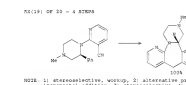
L4 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(18) OF 20 - 3 STEPS



NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective, workup
CON: STEP(1) 1) 0 deg C; 75 minutes, room temperature
STEP(1) 2) 0 deg C; 8 hours
STEP(2) 1) 0 deg C; 1 hour, room temperature
STEP(2) pH 14
STEP(3) 1) 0 deg C; 16 minutes
STEP(3) 2) 0 deg C; 48 deg C
STEP(4) 1) 0 deg C
STEP(4) pH 14

RX(19) OF 20 - 4 STEPS



NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective, 4) stereoselective
CON: STEP(1) room temperature -> 90 deg C; 3 days, reflux
STEP(2) 1) 0 deg C; 75 minutes, room temperature
STEP(2) 2) 0 deg C; 8 hours
STEP(3) 1) 0 deg C; 1 hour, room temperature
STEP(3) 2) pH 14
STEP(4) 1) 0 deg C; 13 minutes
STEP(4) 2) 19 hours, 30 deg C
STEP(5) 1) 0 deg C
STEP(5.1) pH 14

L4 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(11) OF 20 - 2 STEPS

NOTE: 1) alternative preparation shown, incremental addition, 2) stereoselective
CON: STEP(1) room temperature -> 50 deg C; 75 minutes, room temperature
STEP(1.1) 0 deg C; 8 hours
STEP(1.2) 0 deg C; 1 hour, room temperature
STEP(1.2) pH 14

RX(14) OF 20 - 3 STEPS

NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective
CON: STEP(1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours
STEP(3.1) 0 deg C; 10 hours
STEP(3.2) 0 deg C
STEP(3.3) pH 14

RX(15) OF 20 - 3 STEPS

NOTE: 1) stereoselective, workup, 2) alternative preparation shown, incremental addition, 3) stereoselective
CON: STEP(1.1) room temperature -> 50 deg C; 3 days, reflux
STEP(2.1) 0 deg C; 75 minutes, room temperature
STEP(2.2) 0 deg C; 8 hours
STEP(3.1) 0 deg C; 1 hour, room temperature
STEP(3.2) pH 14

L4 ANSWER 7 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 149178772 CASREACT
TI Process for production of mirtazapine
IN Kawamura, Hiroyuki; Kimura, Eiji
PA Sumitomo Chemical Co., Ltd., Japan
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO	DATE
PI WO--2008114691	A1	20080925	2008WO-JP054618	20080312
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BI, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA			
JP--2008233842	A	20081001	2007JP-0060575573	20070322
AU--2008237947	A1	20080925	2008AU-2008237947	20080312
CA----2ae1f8e	A1	20080925	2008CA-2ae1f8e	20080312
EP--2261237	A1	20101215	2008EP-0723122	20080312
ES--2361338	T3	20110617	2008ES-0723122	20080312
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR				
CN--101luiu	A	20090203	2008CN-0F000074	20080312
US-20100039934	A1	20100204	2009US-0661396	20090330
PRAI 2007JP-0060575573		20070322		
2008WO-JP054618		20080312		

AB Claimed is a method for preparing mirtazapine characterized by diluting a reaction liquid obtained by ring-closing reaction of 2-(4-methyl-2-pyrenylpiperazin-1-yl)pyridine-3-methanol (I) with concentrated sulfuric acid in the presence of water with a water-soluble organic solvent in the presence of propanol, extracting mirtazapine into propanol, and crystallizing mirtazapine from the resulting extract. Thus, 7 167.4 g (0 82 mol) was added in portions over about 3 h to 2 91% sulfuric acid 828 g at 0 acti at 36°C to 40°C; the reaction mixture was stirred for about 4 h at 35°C to 40°C, cooled to room temp., and 1 656 g of the reaction portion of this reaction liquid (240 g) was added dropwise to water 626 g, the reaction flask was washed with 98% sulfuric acid 35 5 g which was then added to the diluted liquid; 28% aqueous NaOH solution 438 0 g was added dropwise to the diluted liquid at 32°C to 34°C to adjust the pH to 1 5 to 2 0, and 2-propanol 1 656 g was added; the resulting mixture was stirred for 69 min at 30°C to 33°C, filtered, and washed with water 168 g, the filtrate was divided into 2 portions' 1-propanol 5i g was added to one portion 475 g; 29% aqueous NaOH solution (53 6 g) was added dropwise to the above liquid to adjust the pH to 11 5; the mixture was allowed to sep into 2 layers, and the aqueous layer was removed; 1 g of activated carbon Taiko Layer' this liquid was stirred for 15 min at about 30°C with elimina A-11 (Sumitomo Chemical Co.) 4.8 g, charcoal 1 4 g was added, and the resulting mixture was stirred for 15 min, the mixture was filtered, and washing was done with 1-propanol 14 g; the filtrate was evaporated under reduced pressure to concentrate to about 1 5 times; 1-propanol 7 5 g was added, and the mixture was heated to 44°C; seplum 15 g was added, mirtazapine seed crystals were added at about 53°C; the resulting mixture was kept for 1 h at 50°C. The above mixture was cooled over 6 h to 3°C to give mirtazapine crystals 21 2 g (yield 89%; purity (HPLC) 99 99%). Mirtazapine is a known antidepressant.

L4 ANSWER 7 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

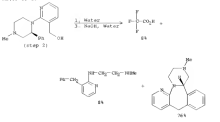
RX(1) OF 1

CON: STAGE(1) 4 hours, 20 - 40 deg C
STAGE(2) 1.5 - 31 deg C, pH 1.5

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 149:294755 CASREACT
TI Asymmetric synthesis of (S)-mitragynine: unexpected racemization through an aromatic spiro-attack mechanism
AU van der Lubbe, Marcel; Bursteen, Judith; Kaspersen, Frans; Kemperman, Gerrit
CS Department of Process Chemistry, Organon' N. V., part of Schering-Plough, Oss, 5340 BH, Neth.
SO European Journal of Organic Chemistry (2008), (17), 2989-2997
CODEN: EJOCFK; ISSN: 1434-193X
PB Wiley-VCH Verlag GmbH & Co. KGaA
DT Journal
LA English
AB An asym. synthesis of (S)-mitragynine has been achieved from the synthesis of the racemate by using (S)-1-methyl-3-phenylpiperazine as the resolving material. Unfortunately, significant racemization was encountered in the last step of the synthesis when the free base was treated with aq. mineral acid, by concentrated sulfuric acid. A significantly higher ee was observed when polyphosphoric acid (PPA) was used instead. A remarkable correlation between the amount of PPA used and the ee of the product was revealed, namely, an increase in the ee upon decreasing the amount of PPA. This trend was reversed in the case of sulfuric acid, where racemization was observed upon lowering the amount of PPA. The racemization and formation of a side-product can be explained by an ipso-attack mechanism during the electrophilic aromatic ring-closure reaction. This mechanism was supported by a mechanistic study using a deuterium-labeled substrate.

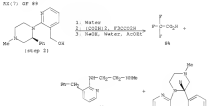
RX(6) OF 89



NOTE: regioselective, 3-Benzyl-2-[(3-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation steps, enantiomeric excess depends on type and equiv. of acidic reagent and on solvent, optimization study, optimized on solvent, optimized on equiv. of polyphosphoric acid (PPA) used first stage, optimized on reaction time, polyphosphoric acid (PPA) used first stage
CON: STAGE(1) 140 deg C
STAGE(2) 18 hours, 130 deg C
STAGE(3) pH 8

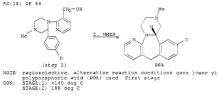
L4 ANSWER 9 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(7) OF 89



NOTE: regioselective, 3-Benzyl-2-[(3-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation steps, optimization study, optimized on equiv. of polyphosphoric acid (PPA) used first stage
CON: STAGE(1) 140 deg C
STAGE(2) 18 hours, 130 deg C

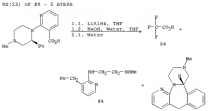
RX(18) OF 89



NOTE: regioselective, alternative reaction conditions gave lower yield, polyphosphoric acid (PPA) used first stage
CON: STAGE(1) 140 deg C
STAGE(2) 180 deg C

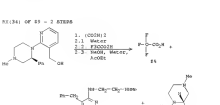
L4 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(23) OF 89 - 2 STEPS



NOTE: 2) regioselective, 3-Benzyl-2-[(3-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation steps, enantiomeric excess depends on type and equiv. of acidic reagent and on solvent, optimization study, optimized on solvent, optimized on equiv. of polyphosphoric acid (PPA) used first stage, optimized on reaction time, polyphosphoric acid (PPA) used first stage
CON: STAGE(1.1) overnight, room temperature
STAGE(1.2) overnight, reflux
STAGE(1.3) 18 deg C -> reflux, 30 minutes, reflux
STAGE(2.1) 140 deg C
STAGE(2.2) 18 hours, 130 deg C
STAGE(2.3) pH 8

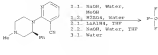
RX(34) OF 89 - 2 STEPS

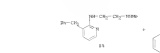


NOTE: 1) no exptl detail, 2) regioselective, 3-Benzyl-2-[(3-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation steps, optimization study, optimized on equiv. of polyphosphoric acid, polyphosphoric acid (PPA) used first stage
CON: STAGE(2.1) 140 deg C
STAGE(2.2) 18 hours, 130 deg C

L4 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(40) OF 89 - 3 STEPS

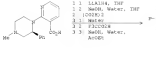


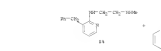


NOTE: 3) regioselective, 3-benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv of polyphosphoric acid, reagent, stoichiometry, temperature and reaction time.

CON: 3.1. NaOH, Water, MeOH
3.2. NaBH4, Water
3.3. Silica
STEP(3.1) 55 degrees, 90 deg C, pH 9.0 - 9.5
STEP(3.2) overnight, room temperature
room temperature -> 10 deg C
STEP(3.3) 10 % MeOH in DCM, 30 minutes, reflux

RX(44) OF 89 - 3 STEPS





NOTE: 3) regioselective, 3-benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv of polyphosphoric acid, reagent, stoichiometry, temperature and reaction time.

CON: 3.1. NaOH, Water, MeOH
3.2. NaBH4, Water, THF
3.3. Silica
STEP(3.1) 55 deg C, 90 deg C -> reflux, 3 days, reflux
STEP(3.2) 16 hours, 130 deg C, pH 9.0 - 9.5
STEP(3.3) 10 % MeOH in DCM, 30 minutes, reflux

L4 ANSWER 6 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

NOTE: 2) no expll. detail, 3) regioselective, 3-benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv of polyphosphoric acid, reagent, stoichiometry, temperature and reaction time.

CON: STEP(2.1) overnight, room temperature
room temperature -> 10 deg C
STEP(2.2) 3 hours, reflux
STEP(3.1) <140 deg C
STEP(3.2) 16 hours, 130 deg C

RX(45) OF 89 - 4 STEPS

NOTE: 3) no expll. detail, 4) regioselective, 3-benzyl-2-(2-methylaminoethyl)aminopyridine isolated by HPLC as a trifluoroacetate, alternative preparation shown, optimization study, optimized on equiv of polyphosphoric acid, polyphosphoric acid (PPA) used first stage

CON: 4.1. NaOH, Water, MeOH
4.2. NaBH4, Water
4.3. Silica
STEP(4.1) 55 deg C, 90 deg C -> reflux, 3 days, reflux
STEP(4.2) 16 hours, 130 deg C, pH 9.0 - 9.5
STEP(4.3) 10 % MeOH in DCM, 30 minutes, reflux

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

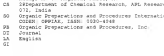
L4 ANSWER 7 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(8) OF 13 - 3 STEPS

CON: STEP(1.1) 7 hours, room temperature -> 130 deg C; 130 deg C -> 90 deg C
STEP(1.2) pH 6.5 - 7
STEP(2.1) 18 hours, 0 deg C; 0 deg C; 55 deg C -> 10 deg C
STEP(3.1) 18 hours, 90 deg C; 3 hours, reflux
STEP(3.2) <90 deg C, pH 10.5

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 16 CASREACT COPYRIGHT 2010 ACS on STN



L4 ANSWER 9 OF 16 CASREACT COPYRIGHT 2010 ACS on STN

AN 148:97470 CASREACT

TI Improved synthesis of mirtazapine

AU Reddy, M. Venkat Ramana; Reddy, N. J. Nanda, V. K.; Sivakumaran, M.; Reddy, A. V. Raghava, Yadla, A.

CS 24Department of Chemical Research, APL Research Centre, Hyderabad, 500 072, India

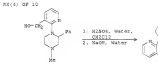
SO Organic Preparations and Procedures International (2007), 39(4), 395-402 CODEN: OPPIBF; ISSN: 0030-4948

PB Organic Preparations and Procedures, Inc

DT Journal

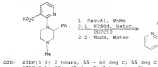
LA English

GI



AB A known 4-step sequence for the preparation of mirtazapine (I), starting from 2-chloro-3-pyridinecarbonitrile and 1-methyl-3-phenylpiperazine, was improved at every stage. The new procedure offers advantages of higher yields, mild reaction conditions, easier work-up, and shorter reaction times

RX(4) OF 10



CON: STEP(3.1) 28 - 42 deg C; 3 hours, reflux
STEP(3.2) <42 deg C, pH 10.5

RX(7) OF 10 - 2 STEPS

CON: STEP(3.1) 2 hours, 55 - 60 deg C; 55 deg C -> 10 deg C
STEP(3.2) 28 - 42 deg C; 3 hours, reflux
STEP(3.2) <30 deg C, pH 10.5

L8 ANSWER 9 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS

CON: STEP(1.1) 7 hours, room temperature -> 130 deg C; 130 deg C -> 90 deg C
STEP(1.2) pH 6.5 - 7
STEP(2.1) 18 hours, 0 deg C; 0 deg C; 55 deg C -> 10 deg C
STEP(3.1) 18 hours, 90 deg C; 3 hours, reflux
STEP(3.2) <90 deg C, pH 10.5

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

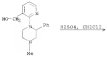
L4 ANSWER 10 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 148:230243 CASREACT
TI An improved process for the preparation of mirtazapine
IN Handa, Vijay Kumar; Rao, Divvela Venkata Naga Srinivasa, Suvvakumar, Manthatisudhakar
PA Aurobindo Pharma Limited, India
SO PCT Int. Appl., 17pp.
CODEN: PIXXD2
CT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI IN--2006001794	A	20080602	2006IN-DEL00794	20060809
IN------005196	A1	20100629		
PRAI 2006IN-DEL00794		20060809		

OS

AB This invention relates to an improved process for the preparation of Mirtazapine (1), which involves the cyclization of pyridine carbinol compound, with chloric acid in an organic solvent.

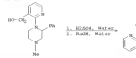
RX(1) OF 1



CON: 3 hours, 30 - 40 deg C

L4 ANSWER 11 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 148:164666 CASREACT
TI Synthesis of mirtazapine
AU Sun, Ping-hua; Chen, Wei-wei; Gao, Jin-ling; Jin, Qian-ying; Xu, Yi
CS Faculty of Pharmacy, Jiangsu University, Zhenjiang, 212013, Peop. Rep. China
SO Zhongguo Yiyao Zazhi (2008), 43(2), 140-142
CODEN: ZYZAEC; ISSN: 1001-0408
PB Zhongguo Yiyao Zazhi Zazhishe Youxian Gongsi
DT Journal
LA Chinese
AB A synthesis of mirtazapine (I) via 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrrolo[2,1-c][1]benzazepine(II), an antidepressant agent, is reported. Mirtazapine was obtained via several steps involving cyclization, reduction, hydrolysis, etc. using Na benzylformate as a starting material. The chemical structure of the mirtazapine was confirmed by IR, MS, and 1H-NMR. The overall yield was 37.4%. Thus, an improved synthetic procedure of mirtazapine was obtained.

RX(1) OF 21



(step 1)

NOTE: 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STAGE(1) room temperature; 6 hours, 35 - 45 deg C
STAGE(2) cooled, pH 10

RX(19) OF 21 + 3 STEPS

NOTE: 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STEP(1.1) 2.5 hours, reflux; reflux -> room temperature
STEP(1.2) room temperature
STEP(2.1) room temperature; 6 hours, 35 - 45 deg C
STEP(2.2) cooled, pH 10

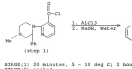
L4 ANSWER 12 OF 16 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(15) OF 21 + 3 STEPS

NOTE: 3) 37.4% yield over 6 steps is from benzoylformic acid methyl ester
CON: STEP(1) 13 hours, reflux
STEP(2.1) 2.5 hours, reflux; reflux -> room temperature
STEP(2.2) room temperature
STEP(3.2) room temperature; 6 hours, 35 - 45 deg C
STEP(3.2) cooled, pH 10

L4 ANSWER 13 OF 16 CASREACT COPYRIGHT 2010 ACS on STN
AN 147:511892 CASREACT
TI Synthesis of potential related substances of mirtazapine
AU Rao, Divvela Venkata Naga Srinivasa; Suvvakumar, Manthatisudhakar; Handa, Vijay Kumar; Sivaramana, Nemmanikkanderam; Naidu, Andra
CS Chemical Research Department, APL Research Centre, Hyderabad, 500 072, India
SO ARKIVOC (Gainesville, FL, United States) (2006), (15), 127-132
CODEN: ARKIAD; ISSN: 1551-7012
URL: http://www.arkat-usa.org/ARKIVOC/JOURNAL_CONTENT/researchpics/2006/16-2187EPS10ark970publishedOnWebmanuscript.pdf
PB Arkat USA Inc.
DT Journal; (online computer file)
LA English
AB The synthesis of three contaminants of mirtazapine, formed during the preparation of mirtazapine bulk drug, is described. The products are 5-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepin-3-oxide, 1-(3-methylpyridyl-2)-1-3-phenyl-4-methylpiperazine, and 1-(3-methyl-1-oxidopyridyl-2)-1-3-phenyl-4-methylpiperazine-1,5-a]pyrido[3,2-f]azepine. The structures of these compds. were established on the basis of spectral data (IR, 1H-NMR and MS).

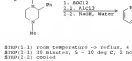
RX(5) OF 7



(step 3)

CON: STAGE(1) 30 minutes, 5 - 10 deg C; 3 hours, 15 - 30 deg C
STAGE(2) cooled

RX(7) OF 7 + 3 STEPS



CON: STEP(1.1) room temperature -> reflux, 4 hours, reflux
STEP(2.1) 30 minutes, 5 - 10 deg C; 3 hours, 15 - 30 deg C
STEP(3.2) cooled

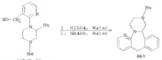
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 146:462287 CASREACT
TI Process for preparation of mirtapine
IN Kang, Yanlong, Qu, Feng, Liu, Kun
PA Beijing D-Venturepharm.T. Corp., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 7pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN-----1939918	A	20070404	2005CN-010105688	20050930

PRAI 2005CN-010105688 20050930
AB The present invention pertains to a process for the preparation of mirtapine, which comprises: (1) reacting 3-hydroxymethyl-2-chloropyridine and 1-methyl-3-phenyl-piperazine for 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine in an aprotic solvent at 10-180 °C; (2) cyclization of the piperazine intermediate obtained above for mirtapine. The process has the advantages of simple operation, low-cost substrates, high yield, high product quality, and hence is convenient for mass production

RX(1) OF 3



(step 1)

NOTE: reaction from p 5 in patent
CON: STAGE(1) room temperature -> 10 deg C; 4 hours, room temperature;
1.5 - 2.0 hours, room temperature -> 50 deg C
STAGE(2) pH 9.0

AN 146:380013 CASREACT
TI Preparation of optically active 1-methyl-3-phenylpiperazine and preparation of optically active mirtazapine from said piperazine derivative
IN Maeda, Hiroshi, Matsui, Kozo, Itaya, Nobushige
PA Sumitomo Chemical Company, Limited, Japan
SO PCT Int. Appl., 72pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2007035003	A1	20070329	2006WO-JP0319625	20060925

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP--2007284416	A	20071101	2006JP-000259194	20060925
EP-----1930325	A1	20080611	2006EP-000810980	20060925

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US-20090275749	A1	20091105	2008US-000067677	20080321
IN---200802019	A	20090227	2008IN-000002019	20080424
CN---101312955	A	20081126	2006CN-080043136	20080519

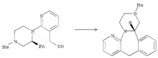
PRAI 2005JP-000278758 20050926
2006JP-000079486 20060322
2006WO-JP0319625 20060925
OS MARPAT 146:380013
GI

I

AB Optically active 1-methyl-3-phenylpiperazine is prepared by reaction of MeN(Z1)CH2CO2H [Z1 = protecting group for amino group] with optically active phenylglycine derivative I [R1 = (un)substituted alkyl, (un)substituted cycloalkyl, (un)substituted aralkyl; the carbon atom with the asterisk is an asym. carbon atom], followed by removal of the Z1 protecting group, cyclization, and reduction. The process for producing optically active mirtazapine from I is also disclosed. Thus, hydrogenation of (S)-N-[N-benzyloxycarbonylsarcosyl]phenylglycine Me ester [prepared from N-benzyloxycarbonylsarcosine and (S)-phenylglycine Me ester hydrochloride] gave (S)-N-sarcosylphenylglycine Me ester (II); cyclization of II gave (S)-1-methyl-3-phenylpiperazine-2,5-dione (III); reduction of III gave (S)-1-methyl-3-phenylpiperazine.

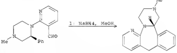
 (Continued)

RX(10) OF 42



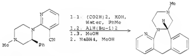
NOTE: literature preparation

RX(18) OF 42 - 2 STEPS



NOTE: 2) literature preparation
CON: STEP(1.1) 30 minutes, 5 deg C; 30 minutes, 5 deg C

RX(30) OF 42 - 3 STEPS

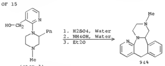


NOTE: 3) literature preparation
CON: STEP(1.1) 1 hour, 25 - 30 deg C
STEP(1.2) -67 - -52 deg C; 2 hours, -64 - -44 deg C
STEP(2.1) 30 minutes, 5 deg C; 30 minutes, 5 deg C

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 146:100636 CASREACT
TI Synthesis of antidepressant-mirtazapine
AU Zhang, Tao; Wu, Fan-hong
CS School of Chemistry and Pharmaceutics, East China University of Science and Technology, Shanghai, 200237, Peop. Rep. China
SO Huadong Ligong Daxue Xuebao, Ziran Kexueban (2006), 32(3), 318-320, 326
CODEN: HLIXEV; ISSN: 1006-3080
PB Huadong Ligong Daxue Xuebao Bianjibu
DT Journal
LA Chinese
AB Mirtazapine [i.e., 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine] was prepared by a seven-step reaction, namely nucleophilic ring-opening reaction, chlorination, cyclization, nucleophilic substitution, hydrolysis, reduction and cyclization from styrene oxide and N-methylethanolamine as the starting materials, with overall yield of 22. 6%. The structure of mirtazpine was confirmed by 1H-NMR (H1-NMR) and MS(mass spectrum), and the purity was 99.79% by HPLC

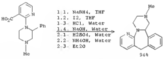
RX(1) OF 15



(step 1)

NOTE: 23% overall yield from 2-phenyl-Oxirane
CON: STAGE(1) room temperature; 4 hours
STAGE(2) cooled, basify

RX(9) OF 15 - 2 STEPS



NOTE: 2) 23% overall yield from 2-phenyl-Oxirane
CON: STEP(1.1) room temperature
STEP(1.2) 30 minutes, 0 - 5 deg C; 1 hour, room temperature;
5 hours, reflux
STEP(1.3) 30 minutes, room temperature
STEP(1.4) room temperature, basify
STEP(2.1) room temperature; 4 hours
STEP(2.2) cooled, basify

L4 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN (Continued)

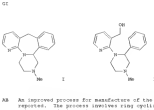
RX(13) OF 15 - 3 STEPS

NOTE 3: 53% overall yield from 2-chenyl-chalcone
CON: STEP(1.1) room temperature -> 100 deg Q; 32 hours, 100 deg Q; 8 hours
STEP(1.2) neutralized
STEP(2.1) room temperature
STEP(2.2) 94 minutes, 0 - 5 deg C; 3 hour, room temperature
STEP(3.1) 91 minutes
STEP(3.2) 30 minutes, room temperature
STEP(4.1) room temperature, cool-fy
STEP(5.1) room temperature; 4 hours
STEP(5.2) cooled, Sonify

L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
AN 144:173916 CAPLUS
TI Improved process for the manufacture of mitteramine by acid-induced ring closure of an alcohol precursor in selected solvents
IN Arnaiz Aguiar, Carmen
PA Esteve Pharmaceuticals, S.A., Spain
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO---2006093182	A2	20060114	2005WO-EP053493	20050719
WO---2006093182	A3	20060413		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
ES---2268361	A1	20060401	2004ES-00001854	20040722
RS---2288361	A1	20070601		
AU---2005226761	A1	20060106	2005AU-00026761	20050719
CA---2572831	A1	20060106	2005CA-02572831	20050719
EP---1765810	A2	20070328	2005EP-00767847	20050719
EP---1765810	B1	20081126		
R: AL, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
BR---2005013571	A	20080506	2005BR-00013571	20050719
JP---2008506775	T	20080306	2006JP-00527847	20050719
AT-------383850	T	20080115	2005AT-00767847	20050719
RS---2316520	T3	20090501	2006RS-00577847	20050719
AR---------50864	A1	20061003	2006AR-00103822	20050721
IN---2007DN0175	A	20070803	2007IN-00000175	20070108
NO---2007005847	A	20070525	2007NO-00705847	20071113
HR---2007000725	A	20070523	2007HR-00000725	20071214
MX---2007000726	A	20070712	2007MX-00000726	20070116
US-2008102789%	A1	20080808	2007US-00636365	20071214
PRAI 2004ES-00001804	20040722			
2005WO-EP053493	20050719			

GI



AB An improved process for manufacture of the antidepressant mitteraplne (I) is reported. The process involves ring cyclisation of six II in selected solvents, and gives mitteraplne in an industrial scale, for pharmaceutical use, in crystalline and amorphous forms. Suitable solvents include halogenated cyclohexanes (especially CHCl3), hydrocarbons, and water. Some prior art methods involve addition of concentrated HCl04 to acid to, giving inefficient stirring and difficult reaction control. Some prior methods also involve

L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN (Continued)
CM(3 with (which leads to impurities), organ- from ether (efficient on a large scale), and recrysta- from petroleum ether 40-60 (also difficult on a large scale). The prior art methods are not suitable for the large scale also disadvantageous in an industrial setting. Moreover, the prior art methods do not always lead to pharmaceutical grade t. Six examples of the livesolin process are given. For instance, 22.2 kg of 94.10% HIB64 was added to a mix- of 3 5 kg IT and 2.5 kg deionized H20 at <80°, and 0.5 kg of 30% NaOH was added to pH 12.5-13.5. The mixture was cooled from temp., HCl2 with cold water at <20°, and distributed between PhMe and 364 IBHOH (pH to 8.5-9.3). After repeated extn. with PhMe, the PhMe phases were combined, washed with H20, dried with NaSO4, filtered, decolorized twice with active C, filtered, and evapd. at >60°. Crystn. from PhMe/hexane (1:3) afforded 19.5 kg of mitteraplne. Reported: from Hisbe, and dried in manu (40-60°, H10% endp) to give 4.7 kg product (92% yield) with HPLC purity 97.7%. PhMe below detection limit of 100 ppm, and EtOAc 899 ppm.

RX(1) OF 1

NOTE: optimization study, workup
CON: STAGE(1) 3.33 hours, 35 - 40 deg C; 40 deg C; 7 hours, 40 deg C

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

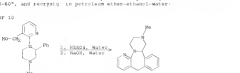
=> d bib abs crd 17 tot

L1 ANSWER 1 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 143:7725 CASREACT
TI Preparation of muscarinic antidepressant
IN Yang, Yanbo; Gao, Baoxin; Chen, Xiaonan; Jin, Huyun
PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China
SO Zhongyi Huaishi Zhengqiyu Gongkan Zhuanmingpin, 8 pp.
CODEN CHOOBY
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN------1439419	A	20030716	2003CN-10014561	20031229
PRAI 2002CN-10014561		20021230		

AB The making comprises substituting 1-methyl-3-phenylpiperazine with 3-(2-halo-1-propoxy)-1-methyl-4-phenylpyridine, reducing 3-(2-halo-1-propoxy)-1-methyl-4-phenylpiperazine, reducing with Raney Ni/NaBH2Cl in water-acetic acid-pyridine mixed solvent at 50-60° to obtain 3-(3-furanyl-3-pyridyl)-1-methyl-3-phenylpiperazine, reducing with NaBH4 in KOH in air at room temperature, cyclizing with concentrated HISO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.

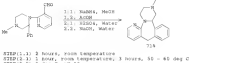
RE(4) OF 10



(step 3)

CON: STAGE(1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STAGE(2) 0 deg C, pH 10

RE(7) OF 10 - 3 STEPS



CON: STEP(1.1) 1 hour, room temperature
STEP(1.2) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(2.1) 0 deg C, pH 10

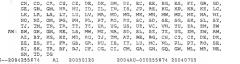
L7 ANSWER 1 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RE(9) OF 10 - 3 STEPS

CON: STEP(1.1) 5 hours, 50 - 60 deg C
STEP(1.2) pH 10
STEP(2.1) 1 hour, room temperature
STEP(2.2) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(3.1) 0 deg C, pH 10

L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 143:134623 CASREACT
TI Preparation of enantiomerically pure (R)-citalopram
IN Andersson, Per Gunnar; Bakker, Wim Van De Vec, Antonius Antonius Martinus; Hengeveld, Severine Susanna
PA Axis Genet N V , Neth
SO PCT Int. Appl., 34 pp
CODEN PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2005105810	A1	20051110	2004WO-EP050397	20040503
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU--2004318875	A1	20051110	2004AU-2004318875	20040503
AU--2005238411	B2	20051006		
CA------2531146	A1	20051110	2004CA-2531146	20040503
EP------1740555	A1	20070110	2004EP-2004729388	20040503
EP------1740555	B1	20081217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN------1832210	A	20060914	2004CN-80053489	20040503
CN--101698726	C	20091111		
NZ--2005216417	A	20060929	2004NZ-2005216417	20040503
NZ--2005216417	B	20080328	2004NZ-2005216417	20040503
AR------2418241	A1	20041859	2004AR-2004100137	20040702
JP--2007512237	T	20070510	2004JP-2006511224	20040503
RS------2006006	CB	20080620	2004YU-2006000505	20040503
AT------1389648	T	20080715	2004AT-2004729388	20040503
PT------1740555	T	20090330	2004PT-2004729388	20040503
ES------2307183	T3	20081016	2004ES-2004729388	20040503
IL------179849	A	20131031	2004IL-2004729388	20040503
US------2285	B	20061107	2004US-2006000505	20040503
HR--2006000519	AB	20061228	2004HR-2006000519	20040503
NO--2006005256	A	20061201	2004NO-2006005256	20040503
ZA--2006000518	A	20070131	2004ZA-2006000518	20040503
US--2006229356	A1	20061012	2004US-2006000505	20040503
IN------2006DN02058	A	20070831	2004IN-2006DN02058	20040503
IN------2009MN	A1	20091227		
CN--101698726	A	20100428	2009CN-80000205	20040503
NO--2009005256	A	20060504	2004NO-2009005256	20040503
LV------1349	B	20061020	2004LV-2006000505	20060106
HK------1146641	A1	20090821	2004HK-2010100132	20060821
PRAI EP2003-10011209		20030703		
2004WO-EP050397		20040503		
OS MARPAT 143:134623				
GI				



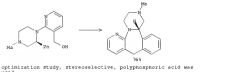
AB (S)-Citalopram was prepared using a ring closure reaction of (R)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent. Thus, (R)-I was prepared from (S)-(1-(3-(4-cyanophenyl)-3-pyridyl)-4-methyl-3-phenylpiperazine, I (X = OH), was dissolved in N-methylpyrrolidinone and polyphosphoric acid was added.

L7 ANSWER 2 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)
The title compd. was obtained in 48% yield with 99.3% ee.

RE(1) OF 2

NOTE: optimization study, stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RX(2) OF 2

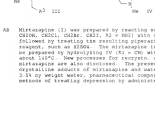


NOTE: stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RE(CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 1 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 138:304301 CASREACT
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Steiger, Claudio; Lineham, Anita; Finkelstein, Nina
IN
SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 542,685.
CODEN USXXCO
DT Patent
LA English
FAN.CNT 1

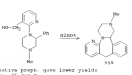
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US-20031040417	A1	20030613	2002US-00306244	20021029
	CN------1675564	A	20050928	2003CN-80104288	20030618
	CN------1680374	A	20051012	2005CN-01000499	20050617
	CN------1680375	A	20051012	2005CN-01000500	20050617
	US------20051158	A1	20050512	2003US-00306846	20031706
	US------8505149	B2	20090408		
	US-20030809%4	A1	20080509	2003US-00283993	20031030
	US------8545961	B2	20031639		
	US-20040102%3	A1	20040527	2003US-00534857	20030315
	US-20040102451	A1	20040527	2003US-00534857	20030315
	US-20040144%1	A1	20040729	2003US-00534857	20030315
	US-20040144511	A1	20040729	2004US-00000%37	20040108
	US-20040144511	A1	20040729	2004US-00000%37	20040108
	AU-2003201127	A1	20030407	2003AU-00201117	20030315
PRAI	1999US-0153301P		19990916		
	2000US-0232685P		20000914		
	2001US-00051405		20010418		
	2002AU-00006957		20020108		
	2002CN-10067074		20020418		
	2002US-00091846		20020704		
	2002US-00306%93		20021030		
	2002US-00306846		20021030		
OS	MARPAT 138:304301				
GI					



AB Mirtazapine (I) was prepared by reacting substituted pyridine II (R1 = CH3ON, CH3CL, CH2Br, CAEI, R2 = NH2) with compound III (R3 = Cl, F, Br, I) followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CH3O) may be prepared by the reaction of III with 1-methyl-3-phenylpiperazine at about 110°C. New processes for recrysin. of I from crude mirtazapine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.1% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.

L7 ANSWER 3 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(3) OF 4



NOTE: alternative progn. gave lower yield; CON. 4 hours, 35 deg C

L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN

L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
TI Methods for the preparation of mirtazapine intermediates
IN Lineham, Anita; Steiger, Claudio
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 31 pp.
CODEN PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO-2002070513	A1	20020912	2002WO-US004340	20020214
	WO-2002070513	A9	20021121		
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CA------2384164		A1	20020912	2002CA-02384164	20020214
AU-2002241130		A1	20020919	2002AU-00241130	20020214
US-20020188138		A1	20021205	2002US-00073940	20020214
US------6774330		B2	20040810		
EP------1366033		A1	20031203	2002EP-00707489	20020214
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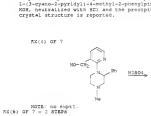
JP-2004518418		T	20040624	2002JP-00569833	20020214
IN------00202777		A	20080429	2003IN-00000777	20030822
PRAI	2001US-0269499P		20010220		
	2001WO-US005160		20010220		
AB	Methods for the preparation of 1-carboxy-2-pyridyl-4-methyl-2-phenylpiperazine (Compd. I) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-cyano-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.



L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

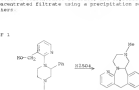
RX(7) OF ? > 3 STEPS

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 136:401780 CASREACT
TI Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
IN Maeda, Takaharu; Soshikawa, Sadatoshi; Iishi, Eiichi
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP-----1509519	A2	20050229	2003EP-0011160	20030528
	EP-----1509519	A3	20050525		
	EP-----1509519	B1	20060111		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US-2003236419	A1	20021230	2003US-0448731	20030527
	US-----6846736	B2	20050125		
	AU-2003240321	A1	20021206	2003AU-0040321	20030430
	CA-----2484135	A1	20021205		
	CN-----1656134	A	20050817	2003CN-0037384195	20030522
	AT-----382626	T	20060115	2003AT-0011160	20030528
	PT-----1509519	E	20060131	2003PT-0011160	20030528
	ES-----2301340	T3	20060516	2003ES-0011160	20030528
	JP-----2005528419	T	20050922	2003JP-0502964	20030523
	JP-----4321410	B2	20090826		
	IL-----166448	A	20070819	2003IL-0166448	20030529
PRAI	2002JP-0163988[P]		20020607		
AB	Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of solvent or (2) substantially free of solvent of vertical volume, and which have an average particle diameter of from 10-50 μm, are described where: use filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.				

RX(1) OF 1

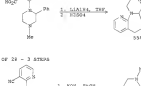


RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(19) OF 28 - 2 STEPS

RX(21) OF 28 - 3 STEPS



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 136:349741 CASREACT
TI A novel method for preparation of piperazine and its derivatives
IN Sebastian, Sunny, Patel, Betal Virendra, Thennati, Rajamanar
PA Sun Pharmaceutical Industries Ltd., India
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--20020637E2	A1	20020808	2002WO-GB000197	20020118
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	IN-----199A7W	A1	20040403	2001IN-0000974	20010427
	AU-2001079949	A	20020211	2001AU-0079949	20010730
	BR-----0113717	A8	20011106	2001BR-0013717	20010730
	CN-----401242	A5	20021015	2001CN-0800011228	20010802
	EP-----1305294	A2	20030502	2001EP-0983739	20011015
	US-----6603910	B2	20030805		
	IN--200000911	A	20040228	2002IN-0000911	20020604
PRAI	2001GB-0000594		20010107		
	2001WO-IN000119		20010629		
GI	GRAPHAI 136:349741				

AB Compds. I (R = H, C1-4 alkyl, phenyl-C1-4 alkyl; R1 = H, Me, (un)substituted phenyl; R2 = H, Me, fluorenylmethyl) are useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting II (R = Cl, F, Br, I) with a compound III in the presence of a base and its derivs., followed by reacting with a reducing agent to yield I. Thus, 1-methyl-3-phenylpiperazine was prepared and used as starting material for preparation of 1,3,5,6,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrrolo[2,1-c][1]benzazepine.

RX(7) OF 28

L7 ANSWER 7 OF 8 CASREACT COPYRIGHT 2010 ACS on STN
AN 133:321900 CASREACT
TI Novel synthesis and crystallization of piperazine ring-containing pharmaceutical active ingredient
IN Singer, Claude; Linsmeier, Anita, Finkelstein, Mona
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--20000673E2	A1	20001026	2000WO-GB001457	20000418
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	AU-2000243517	A	20001102	2000AU-0043517	20000418
	AU-----781221	B2	20050512		
	CN-----1348369	A	20020508	2000CN-0806038	20000418
	EP-----1178856	A2	20020213	2000EP-0919459	20000418
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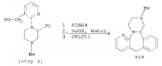
	NO-2001005114	A	20011217	2001NO-0005114	20011018
	US-----6756361	B1	20040629		
	HR-2001032868	A1	20030636	2001HR-0832878	20020123
	SK-2001017681	A1	20020900	2001SK-0001768	20020304
	AP-2002002137	A1	20061007	2002AP-0002137	20050915
	ZA-2001008654	A	20021023	2001ZA-0008654	20011019
PRAI	1999GB-0012014[P]		19990419		
	2000GB-0001874[P]		20000126		
	2000GB-0008187		20000418		
	2000CN-0008787X		20000418		
	2000GB-0008787		20000418		
	2000WO-GB001457		20000418		
	2001GB-0009064		20010706		
	2001IN-0000911X3		20011011		
	2002GB-0002430X3		20020130		
	2002GB-0003444X3		20020213		
GI	GRAPHAI 133.321900				

AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I (R1 = CHCHR, CHCCl, CHCBr, CHCI; R2 = NH2) with compound II (R3 = Cl, F, Br, I) followed by treating the resulting piperazine III

L7 ANSWER 7 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

with H2SO4. The mirtazapine intermediate 1-(3-carboxypyridly-2)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine with KOH at a temp. of at least about 130°C. The present invention also relates to new processes for recrystn. of mirtazapine form crude mirtazapine

RX(1) OF 4



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN

AN 112:139001 CASREACT

TI The synthesis of Org 3770 labeled with tritium, carbon-13 and carbon-14

AU Kaspersen, Frans M.; Van Rooij, Fons A. M.; Sperling, Eric G. M.; Wieringa, Joop H.

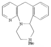
CS Sci. Dev. Group, Organon Int. BV, Oss, 5340 BH, Neth

SO Journal of Labelled Compounds and Radiopharmaceuticals (**1989**), 27(9), 1055-68
CODEN: JLCRD4; ISSN: 0362-4803

DT Journal

LA English

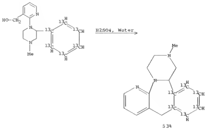
GI



I

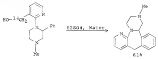
AB The syntheses of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770, I) labeled with 3H (and 2H), 13C and 14C are described. Tritiated I was prepared either by exchange under alkaline conditions with tritiated water or catalytic reductive dehalogenation of a chloro analog with 3H2. 13C-labeled material was obtained in a 7-step synthesis starting from 13C-labeled benzene, whereas I-14C was prepared in a 3-step synthesis starting with 14CO2.

RX(10) OF 118

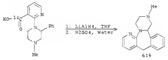


L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

RX(15) OF 118



RX(30) OF 118 - 2 STEPS



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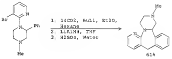
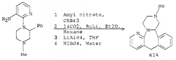


RX(55) OF 118 - 4 STEPS



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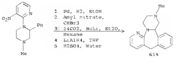

L7 ANSWER 8 OF 8 CASREACT COPYRIGHT 2010 ACS on STN (Continued)

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L7             8 L5-6
L8            16 L4 NOT L7


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